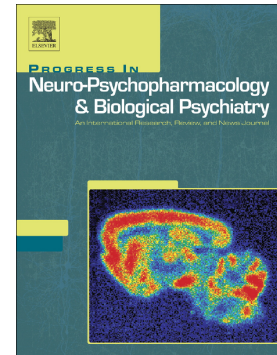


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Julius Schuster, Ellen S. Mitchell



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More Than Just Caffeine: Psychopharmacology of Methylxanthine Interactions with Plant-Derived Phytochemicals

Julius Schuster^{a*} and Ellen S Mitchell^b

^a University of Amsterdam, Swammerdam Institute for Life Sciences, Amsterdam, the Netherlands; ^b PepsiCo R&D, Nutrition Sciences, Purchase, USA

*corresponding author:

Julius Schuster

Email: schust92@gmail.com

Tel. #: +1 518 977 2463

Abstract

In general, preparations of coffee, teas, and cocoa containing high levels of polyphenols, L-theanine and other bioactive compounds selectively enhance mood and cognition effects of caffeine. This review summarizes the bioactive components of commonly consumed natural caffeine sources (e.g. guayusa, mate and camellia teas, coffee and cocoa) and analyzes the psychopharmacology of constituent phytochemicals: methylxanthines, polyphenols, and L-theanine. Acute and chronic synergistic effects of these compounds on mood and cognition are compared and discussed. Specific sets of constituent compounds such as polyphenols, theobromine and L-theanine appear to enhance mood and cognition effects of caffeine and alleviate negative psychophysiological effects of caffeine. However, more research is needed to identify optimal combinations and ratios of caffeine and phytochemicals for enhancement of cognitive performance.

Keywords: tea, cocoa, coffee, *ilex paraguariensis*, *ilex guayusa*, flavanoids, polyphenols, L-theanine, chlorogenic acid, cognition, theobromine

1. Introduction

Methylxanthines (MX) have evolved in many different botanical species because of their pesticidal properties, being toxic for insects and many other potentially harmful pathogens. Humans, however, discovered that consuming MX has diverse health benefits. Today, the main source of caffeine is from brewed coffee, followed by tea, colas and, increasingly, 'energy' drinks. (Table 1).

Table 1. Caffeine content of commonly consumed foods and beverages

Product	Caffeine (mg)
Filter coffee (200 ml)	90
Energy drink (250 ml)	80
Tea* (220 ml)	50
Cola (355 ml)	40
Dark chocolate (50 g)	25
Milk chocolate (50 g)	10

Data retrieved from EFSA¹

*Recent analyses have shown that black, white, and green tea have comparable caffeine content²

Given its widespread consumption, the chronic effects of caffeine have been studied extensively in the past decades. Interestingly, although some reports caution against excessive caffeine consumption, research on moderate caffeine use predominantly reports health-promoting effects of caffeine use and a correlation of reduced mortality.³ For instance, there is a clear association of chronic health benefits from moderate coffee consumption, such as a lower incidence of type-2-diabetes and Parkinson's disease (see umbrella review by Grosso et al.⁴). A review by Panza et al.⁵ found that there was a lower risk of cognitive decline in subjects with higher tea intake. However, well-designed interventional placebo-controlled studies are still missing.

Adverse effects have been attributed to typical levels of caffeine consumption, such as increased nervousness, anxiety, tachycardia and an increase in blood pressure. Yet there is increasing evidence that other constituent compounds in caffeine-containing drinks, for example polyphenols, may antagonize some of the negative effects of caffeine. In fact, recent studies have found that compounds commonly consumed along with caffeine in tea, coffee or cocoa may have synergistic effects with caffeine, or are protective against caffeine's acute and chronic side-effects. The aim of this review is to describe key research on natural sources of caffeine and theobromine, comparing and contrasting psychopharmacological activities of commonly

consumed MX-containing plants. Given that there is little evidence that plant-derived theophylline has cognitive effects, we have focused on caffeine and theobromine. Furthermore, by summarizing research on interactions of other constituent compounds found in MX species (e.g. flavanols, L-theanine, chlorogenic acids) we highlight gaps in current understanding and future research directions in terms of acute and chronic effects of MX interactions.

We chose the form of a narrative review in order to capture all the relevant research. To outline the most relevant bioactive phytochemicals in terms of their neurocognitive effects, this paper reviewed the main sources of MX. Those species that were associated with a high use within specific populations as a food or beverage and had sufficient levels of either caffeine or theobromine (per 100 g) to exert an effect on cognition were included in this review. Secondly, the most relevant bioactive compounds were then reviewed based on their putative acute and chronic effect on mood and cognition. Any papers that used reasonable doses of MX in combination with other phytochemicals such as polyphenols and also used validated (cognitive) measures were included. Both interventional human and animal studies were included in this process, given that the amount of literature on the neurocognitive effects of MX plants and their constituent compounds on humans is still very limited. Because this review focuses on the enhancement of cognitive function in healthy subjects, experiments on clinical populations were excluded. Moreover, in the context of chronic effects, some epidemiological studies (such as from an ageing cohort) were included as well. Lastly, selected substances were assessed in terms of synergistic effects with caffeine or theobromine.

2. Analysis of the most common sources of methylxanthines

2.1. *Camellia sinensis* (green/black/white tea)

The term tea refers to infusions from the *C. sinensis* (*Camellia sinensis* var. *sinensis* and *Camellia sinensis* var. *assamica*) leaves. The many varieties of tea, which are most notably green, black and white, as well as oolong and pu'erh, are the result of different processing methods. For instance, black tea is prepared from fully fermented leaves, oolong tea from partially fermented leaves, and green tea from unfermented leaves. Recent analyses have shown that there is no considerable difference in the caffeine content of green (16.28 mg/g), black (17.77 mg/g) and white tea (16.79 mg/g).² Yet L-theanine content differed significantly, with 6.56 mg/g in green tea (caffeine/L-theanine ratio: 2.79), 6.26 mg/g in white tea (caffeine/L-theanine ratio: 3.07), and 5.13 mg/g of L-theanine in black tea (caffeine/L-theanine ratio: 4.07).

Green tea has the highest polyphenol content and antioxidant properties, followed by black and white tea.⁶ Tea, and especially green tea, has been studied extensively due to numerous constituent flavonoids, flavan 3-ols catechin, gallocatechin, epicatechin, epigallocatechin, epicatechin gallate, and the most bioactive epigallocatechin 3-gallate (EGCG).⁶ However, tea contains also many other compounds such as proanthocyanidins, theaflavins, thearubigins, gallic acid, L-theanine, GABA, and polyamines such as spermidine and spermine,⁷ amongst which L-theanine appears to be most promising.⁸

2.2. *Coffea* sp. (coffee)

Coffee contains numerous different bioactive phytochemicals, most notably 0.8–2.5% caffeine,⁹ but also other MX such as theobromine and theophylline, diterpenes, chlorogenic acids (CGAs), tocopherols, hydroxycinnamic acids, and flavonols.¹⁰ CGA content has been shown to be approximately 34 mg/g in green coffee beans and only 2-7 mg/g in roasted coffee beans.¹¹ Even with the reduced levels of CGA in roasted coffee, people that consume coffee typically intake more CGA than any other polyphenol.¹² Many of the compounds in caffeine, such as catechol, pyrogallol, eicosenoyl-5-hydroxytryptamide as well as CGA, may affect brain function by upregulating dopamine and calcium release.⁴

2.3. *Ilex* sp. (*Mate, guayusa and yaupon*)

Three main MX species of the *Ilex* genus have become popular for their stimulatory properties. All of these originate from the Americas. *Ilex paraguariensis*, also known as yerba mate or mate, is by far the most commonly consumed species, with a long history of use by natives in South America and an increasing popularity in the Western world. Its bioactive phytochemicals are, aside from MX, phenolic acids, flavonoids such as quercetin and rutin, and saponins.³

Fresh mate provides approximately 10-133 mg of CGA, thus it has comparable high levels of CGA as coffee.¹³ However, similar to coffee, roasting reduces CGA content to only 16-41mg (ibid). *Ilex guayusa* has an interesting pharmacological profile, containing L-theanine (1.3 mg/g), theobromine (0.4 mg/g), caffeine (32.8 mg/g) as well as some flavonoids.¹⁴ Thus, the main difference of guayusa to mate lies in its MX composition, containing less caffeine and more theophylline and theobromine. *Ilex vomitoria*, or yaupon, has also a history of consumption and contains twice as much theobromine than caffeine.¹⁵ *I. vomitoria* contains half as much theobromine but over 5 times more caffeine.¹⁵ These New World hollies can be considered as interesting natural alternatives for the conventional sources of caffeine, coffee and tea.

2.4. *Theobroma cacao* (*cocoa*)

Theobroma cacao is the most commonly consumed source of theobromine, yet also contains high concentration of catechins and anthocyanidins. Natural cocoa contains approximately 35 mg/g theobromine, medium processed cocoa contains approximately 8 mg/g, and heavily processed cocoa only approximately 4 mg/g.¹⁶ Unlike most other MX species, *T. cacao* contains more theobromine than caffeine. Cocoa beans are very rich in polyphenols such as catechins and proanthocyanidins, though fermentation, drying and roasting results in considerably lower concentrations in processed cocoa.¹⁷ Numerous other constituent compounds in cocoa have been tenuously linked to cognitive effects, such as phenylethylamine, anandamide, as well as tyrosine and tryptophan. Whilst some of these compounds may have effects in certain circumstances, the concentration of these phytochemicals is not large enough or comparable to other foods.¹⁸

2.5. *Paullinia cupana* (guarana)

Guarana is a traditionally consumed Amazonian stimulant from the *Paullinia cupana* species. The *P. cupana* seeds can contain up to 6% caffeine and other bioactive compounds such as catechins, saponins, and tannins.¹⁹ In a recent intervention study with guarana, researchers found that some procognitive effects of guarana are partially due to the psychoactivity of these constituent phytochemicals.²⁰ More research is needed to confirm these findings. Guarana as well as other sources of MX such as kola nuts are not in the scope of this review since they have comparably limited use (the amounts in energy drinks are miniscule) and there are few studies on cognition. Hence, the analysis in the next section focuses on the main phytonutrients of coffee, tea, mate and guayusa, as well as cocoa.

3. Psychopharmacology of methylxanthine plant phytochemicals

3.1. *Methylxanthines*

Pharmacology of caffeine and theobromine.

Almost all caffeine is absorbed within 45 minutes following oral consumption of a moderate dose (50-250 mg).²¹ Peak plasma concentrations are being reached approximately 30 minutes following the intake of caffeine.²² The half-life is approximately 2.5-5 hours.¹⁸ The cytochrome P450 enzyme CYP1A2 metabolizes over 90% of the plasma caffeine. CYP1A2 gene polymorphism has been shown to alter the expression or activity of the CYP1A2 enzyme,²³ which subsequently results in a large individual variability of caffeine clearance. Urine analyses have shown that caffeine gets mostly metabolized into paraxanthine (78 %) but also theobromine (14 %) and theophylline (9 %).¹⁸ Due to its lipophilic profile, caffeine is capable of crossing the blood-brain barrier. It exerts a number of divergent effects on a cellular level. It is known to block adenosine receptors, act as a phosphodiesterase (PDE) inhibitor, affect the regulation of calcium levels and affect GABA neurotransmission.¹⁸ The main effect of caffeine can be attributed to its antagonistic effect on the adenosine receptors (ARs). The structure of caffeine is very similar to adenosine, which allows it to bind to (all) the A1, A2a, A2b, and A3 ARs. Studies

on A1 and A2a AR knockout mice have shown that the arousal effect of caffeine is dependent on the blockade of A2a and not A1 ARs.²⁴

Theobromine is absorbed more slowly than caffeine and it reaches peak plasma concentrations after 2.5 hours, however the exact time depends on its medium.¹⁸ Administration of isolated theobromine would require 3 hours to reach peak plasma concentrations, whereas theobromine ingested as or with chocolate would take only 2 hours. The clearance rate is approximately half of the caffeine clearance, though chronic (> 4 days) exposure to theobromine results in a significant increase in theobromine clearance.¹⁸ Similar to caffeine, theobromine gets distributed throughout the total body water,¹⁸ thereby suggesting that it has a similarly high blood-brain permeability. Experiments on mice have found theobromine in the brain upon oral administration, albeit the concentrations were only 10% of the plasma concentrations.²⁵ Moreover, theobromine has a 2-3 times lower A1 AR and a 10 times lower A2 AR receptor affinity than caffeine.²⁶ In contrast to caffeine, the nonselective PDE inhibition effect of theobromine appears to be more potent, for instance moderate theobromine doses produce broncho – and vasodilation in humans.¹⁸

Cognitive effects of caffeine and theobromine.

The procognitive effects of caffeine have been studied extensively, especially in terms of reaction time, vigilance, attention, acute and chronic memory effects, executive function, as well as judgment and risk-taking behavior (see review McLellan et al.²⁷), with moderate doses of 100-300 mg being most beneficial. Many studies assessing cognitive performance also found an improvement in the self-reported mood of the subjects (see review Ruxton²⁸).

Theobromine has significantly less arousing properties compared to caffeine,²⁶ which can be explained by its lower AR affinities and its lower blood-brain barrier permeability. Hence, theobromine itself is mainly associated with peripheral effects, most notably causing a decrease in blood pressure and increased heart rate.¹⁸

A few studies, nevertheless, attributed psychoactive properties to theobromine: most notably, experiments by Mitchell et al.²⁹ revealed that a dose of 700 mg theobromine decreased self-reported calmness. Aside from reduced reaction time, Mitchell et al. did not find any acute

improvement in psychomotor performance as measured in the Digit Symbol Substitution Test. However, more recent experiments on mice found that 30 days of theobromine-supplemented diet caused an improvement in motor learning in the three-lever motor learning task.²⁵

Earlier research by Mumford et al.³⁰ reported behavioral effects from theobromine such as an increase in alertness, energy and motivation, but also sleepiness in some subjects. The more interesting properties of theobromine might, however, lie in its synergistic effect with caffeine: Smit & Blackburn³¹ showed that the addition of 19 mg caffeine and 250 mg theobromine increased the liking of chocolate considerably. Although it remains unclear whether this effect can be attributed to the constituent theobromine, Smit & Blackburn attributed this effect to theobromine because caffeine is unlikely to exert behavioral effects at these concentrations.

3.2. Polyphenols

Pharmacology of flavonoids.

Many beneficial health effects of flavonoids have been linked to their powerful antioxidant capacity, yet the cognitive effects of flavonoids are likely caused by other mechanisms.³² Flavonoids have been shown to affect signal cascades that are involved in long term potentiation and the survival of neurons in vitro, however it is unclear whether flavonoids can reach the brain in sufficient levels. It has been shown that flavonoids can cross the blood-brain barrier, for instance anthocyanins from blueberries collected in regions associated with spatial memory such as the hippocampus, the striatum and the cortex.³² Lastly, similar to theobromine, flavonoids have peripheral effects such as vasodilation. Lamport et al.³² suggested that the cognitive effects of flavonoids may be due to regional vasodilation via nitric oxide induction, leading to increased cerebrovascular blood flow.

Cognitive effects of flavonoids.

A recent review by Socci et al.³³ studying the effects of cocoa supplementation found that, most notably, aged subjects benefitted the most from chronic cocoa flavanol intake. Acute effects of cocoa flavanols were mainly observed for tasks involving sustained performance or during

impaired physiological function. Out of seven studies reviewed, five studies found a significant acute cognitive effect from cocoa, with improvements in visual information processing, spatial working memory, concentration and memory as measured in the Serial Threes and Serial Sevens task, and vigilance following sleep deprivation (most notably in women) as measured in the 2-back task.^{34–38} Another study in younger male subjects found an increase in cerebral blood oxygenation, but no change in Stroop task scores.³³ Given that high-flavanol cocoa increases cerebral blood flow in both young and older subjects,^{39,40} it is likely that improved cerebral perfusion is responsible for the acute and possibly also the chronic procognitive effects of flavanols. This effect is induced by nitric oxide-mediated peripheral and central vasodilation and a consequent improvement of cerebral blood flow. In line with this theory, Brickman et al.⁴¹ found that older adults consuming high-flavanol containing cocoa for 3 months showed increased dentate gyrus function as measured in an fMRI. This increase correlated with improved cognitive performance. Given that some studies did not find any improvement,^{36,42} further research should evaluate for what groups and at what doses cocoa flavanols appear to be most beneficial.

Some research suggests that tea catechins, mainly EGCG, elicit cognitive effects as well. EGCG administration has been associated with self-reported calmness and reduced stress in healthy subjects.⁴³ Yet, a more recent review by Dietz & Dekker⁴⁴ could still not find any conclusive evidence on improvements in cognitive performance following the administration of green tea EGCG.

Aside of its antioxidant properties, EGCG enhances cerebrovascular activity by improving endothelial function and enhancing the supply of nitric oxide.⁸ EGCG administration was associated with a significant overall increase in alpha, beta and theta EEG activity.⁴³ Moreover, it increased EEG activity in frontal and central regions such as the frontal gyrus and medial frontal gyrus.⁴³ Yet, the exact cognitive benefit of changes in neurogenesis and cerebral blood flow remain to be understood. For instance, experiments by Wightman et al.⁴⁵ found a decrease in blood flow and a measured lower oxygenated blood and total hemoglobin count in the frontal cortex in subjects receiving 135mg EGCG. Though, no change in cognitive performance was found during these experiments. Discordant effects of flavanols on cerebral blood flow and cognition may be due to differences in doses and ratios of cocoa flavanol

treatments, as well as other compounds in the test products, while subject characteristics and timing of measurements must also be considered.

Pharmacology of chlorogenic acid.

CGA is amongst the most abundant acids in tea and in green coffee extracts as well as in mate.^{13,46} In fact, CGA refers to numerous hydroxyl cinnamic esters.⁴⁶ Only about one third of the CGA content is taken up by the small intestine, whereas the rest is being metabolized and absorbed by the large intestine (ibid). Once circulating in the blood, CGA appears to exert multiple different effects.

Cognitive effects of chlorogenic acid.

CGA is a potent antioxidant and anti-inflammatory compound, which may contribute to its beneficial neurocognitive effects by protecting neurons.⁴⁷ Moreover, chronic administration causes – similar to EGCG – a decrease in blood pressure and improvements in endothelial function by promoting the release of nitric oxide and thromboxane A₂.⁴⁸

Preclinical and clinical findings on CGA support a possible pro-cognitive effect. A review by Heitman & Ingram⁴⁷ found that CGA improved various parameters of cognition in rodents. Most significant were attenuating effects of CGA in animals that experienced cognitive impairment due to diabetes, ischemia, or scopolamine – causing a considerable improvement in memory function. Aside from these neuroprotective effects, some research also outlined general improvements in cognition such as in spatial learning and memory, motor function and decreased anxiety. For instance, Bouayed et al.⁴⁹ found that 20 mg/kg of CGA reduced anxiety in a similar manner as 1 mg/kg diazepam in mice. Meanwhile studies on healthy humans consuming decaffeinated coffee with high or low CGA content found that the high CGA group experienced an improvement of mood.⁵⁰ Similarly, a study by Camfield et al.⁵¹ that compared the effects of decaffeinated coffee to the effect of pure CGA found that the mood-enhancing effects of the decaffeinated coffee blend are most likely due to the constituent CGA. However, improvements in cognitive function occurred only in subjects receiving the decaffeinated coffee blend, whereas

CGA only resulted in lower performance scores compared to placebo.

3.3. *L-theanine*

Pharmacology of L-theanine.

L-theanine occurs in green tea at comparable concentrations as caffeine (3% vs 2-5%).⁸ It takes approximately 50 minutes until peak blood levels are being reached (compared to 30 minutes for caffeine).⁸ Experiments investigating the effect of intragastrically administered L-theanine in rats found that L-theanine passed the blood-brain barrier via leucine-preferring transport.⁵² There, it resulted in the release of serotonin and dopamine, most notably in the hippocampus, hypothalamus and the striatum. Moreover, the release of GABA is most likely responsible for the relaxation-promoting, anxiogenic properties of L-theanine.⁸

Cognitive effects of L-theanine.

Whilst caffeine has mainly been associated with increased wakefulness, L-theanine appeared to have opposite effects, increasing relaxation and calmness at doses of 200 mg.⁴⁴ L-theanine appears to exert its most beneficial effect in combination with caffeine. For instance, the consumption of L-theanine and caffeine resulted in an improved attentional switching (AS) task performance than with caffeine alone.⁴⁴ A systematic review by Camfield et al. investigated 11 studies on the effect of tea constituents such as L-theanine. The authors conclude that the combination of L-theanine and caffeine increased Bond-Lader alertness, attention switching accuracy as well as a small increase in unisensory visual attention.⁸ Though they also suggest that the effect is mainly dependent on the dose of caffeine. Even though the majority of the beneficial effects must be attributed to caffeine, the somewhat opposite, potentially GABA-mediated effects of L-theanine might play an important role in improving the pleasurable effect of caffeine by reducing unpleasant side-effects such as 'jitteriness'. A more recent study by Kahathuduwa et al. found that high (200mg) doses of L-theanine improved recognition visual reaction time performance similarly as caffeine and that a combination had additive effects.⁵³ Although another study by Giles et al. found that caffeine and L-theanine exert opposite effects

on attention under emotional arousal.⁵⁴ These findings suggest that the beneficial effect of L-theanine might be due to its anxiolytic properties. Indeed, previous experiments by Higashiyama et al. (2011) found that L-theanine did only cause significant improvement in attention and reaction time in subjects that exhibited a greater degree of (self-reported) anxiety.⁵⁵ Similarly, experiments by White et al. analyzing the cognitive effect of NeuroBliss®, an L-theanine based nutrient drink, found that the product did not induce any change in cognitive performance.⁵⁶ It did, however, reduce subjective stress response which also correlated with a reduced cortisol response. All in all, further experiments are necessary to study the effect of L-theanine by controlling for trait anxiety and, possibly, also at higher doses.

4. Analysis of methylxanthine + phytonutrient combinations

Caffeine-induced improvements on cognitive performance are well-established, with mainly an acute improvement in basic tests assessing attention, vigilance, or alertness. Yet, the efficacy of caffeine improving higher-order cognitive performance remains unclear.²⁷ Theobromine alone, on the other hand, has not been shown to exert very significant effects on cognitive performance in humans. Albeit recent experiments on adult mice did show that the consumption of theobromine for over 30 days improved motor learning performance and increased cerebral BDNF expression.²⁵ Previously outlined research revealed that isolated doses of caffeine and theobromine exert differential – and possibly less beneficial – effects than MX preparations from plant sources that provide also a number of other phytochemicals. These phytochemicals can contribute to the positive effects of MX-containing foods and beverages in two main ways: on the one hand, they might be responsible for the positive effects, either by themselves or in synergy with caffeine or theobromine. On the other hand, they might alleviate certain adverse effects of caffeine, potentially enabling caffeine-sensitive people to be less negatively affected from caffeine's stimulatory action.

While human data is lacking, rodent studies indicate that MX-containing plants may be effective at alleviating cognitive decline due to aging. For instance, aged (19 months) rats receiving a coffee supplemented diet showed a significantly improved reference memory performance in the Morris water maze.⁵⁷ Follow-up experiments showed that caffeine supplementation alone did not promote enhanced performance. In the following, we will outline findings on the interaction of MX with other polyphenols and how they affect cognition and mood acutely, as well as other chronic effects on the body. These interactions are particularly interesting because natural MX are almost always being taken up in conjunction with polyphenols.

4.1. Acute effects on cognition

4.1.1. Attention

Caffeine and L-theanine.

Improvement in attention, especially in sustained attention, is one of the key pro-cognitive effects associated with caffeine consumption. The combination of L-theanine and caffeine is among the most studied with notable effects on attention (see table 2). A review by Camfield et al.⁸ concluded that the combinations of caffeine (50-100 mg) and L-theanine (100-250mg) increases subjective alertness (measured with the Bond-Lader test). Several studies revealed improvements in attentional performance, such as increases in attention switching accuracy, unisensory visual attention – and unisensory auditory attention accuracy in healthy subjects. For instance, Kahathuduwa et al.⁵³ observed additive effects of the caffeine + L-theanine combination on attention in high doses, most notably on the recognition visual reaction time (RVRT) task. Yet, other studies could not replicate the same findings.

Taken together, published studies indicate that the overall effect of L-theanine on attentional performance appears to be slight and its main effects are modifying to caffeine's activity. Moreover, L-theanine in some circumstances appears to cancel out caffeine's efficacy. For instance, experiments assessing the effects of caffeine (50mg) and L-theanine (100mg) on the maintenance of vigilance during a sustained attention task found that both compounds separately improve sustained attention.⁵⁸ However, the combination did not result in a greater improvement than either one of the compounds alone. A recent experiment by Giles et al.⁵⁴ found that caffeine and L-theanine caused opposite effects on attention under emotional arousal resulting in effects similar to the placebo control group. All in all, although the findings on L-theanine and caffeine modify subjective attention, there is no clear consensus on how the combination affects cognitive performance. Additionally, it should be noted that the natural L-theanine content in tea is much lower than the amounts (of up to 250mg) that have been used in some of these studies.

Caffeine, theobromine and cocoa flavonoids.

There is no evidence that theobromine has an effect on attention by itself.⁵⁹ However, experiments by Smit, Gaffan & Rogers⁶⁰ found that chocolate preparations with low MX content (8 mg caffeine + 100 mg theobromine) caused an improvement in sustained attention (RVIP) compared to chocolate with no MX content. Whilst these experiments prove that sugar and fat did not affect MX absorption, the study design did not control for the possible impact of cocoa polyphenols which might affect MX absorption. Earlier experiments with higher doses of MX found that both 11.6 g cocoa powder (CP), and the equivalent amount of MX (250 mg of theobromine + 19 mg of caffeine) both improved reaction time equally.⁶⁰ Interestingly, only the isolated MX dose caused a significant improvement in sustained attention as measured by RVIP performance. In these experiments, isolated doses of MX caused a stronger procognitive effect in some of the tests than cocoa. A possible explanation for these divergent outcomes could be slower absorption of caffeine when delivered in the form of chocolate (see sections below for further details).

Findings on effects of polyphenols and MX are, at this point, scarce. Experiments by Boolani et al.⁶¹ found that caffeinated cocoa (70mg caffeine, 179 mg theobromine, 499 mg flavanols) caused lower omission errors and improved accuracy in healthy subjects compared to cocoa alone (21 mg caffeine, 179 mg theobromine, 499 mg flavanols), but attentional performance was not better than the caffeine only group. However, Scholey et al.³⁴ found that subjects given high flavanol cocoa improved rapid visual information processing task (RVIP) performance compared to a matched control group. Future experiments should evaluate whether a high dose of flavanols (e.g. 994 mg – as in the experiments by Scholey et al.) plus theobromine causes similar attention effects.

Table 2. Additive effects of caffeine plus constituent compounds on attention.

Combination	Subjects[Age]	Test	Outcome	Additive effects	Reference
L-theanine (250 mg) + caffeine (150 mg)	24 (M=21.3, 18–34)	Simple reaction time (RT), Digit Vigilance (DV) test, Rapid Visual Information Processing (RVIP)	Combination resulted in better simple RT, better RVIP accuracy, but worse DV reaction time	Yes	Haskell et al. (2008) ⁶²
Caffeine (100 mg) + L-theanine (50 mg)	27 (M=28.3, SD=5.34)	Attentional Switch (AS), Memory Task (MT)	Simultaneous increase in response speed and accuracy in AS, reduced susceptibility to distracting stimuli in MT	Yes	Owen et al. (2008) ⁶³
L-theanine (97 mg) + caffeine (40 mg)	29 (M=30.6, 18–45)	AS, Intersensory Attention (IA)	Improved task switching, but not intersensory attention or subjective alertness	Uncertain (mainly affecting executive control)	Einöther et al. (2010) ⁶⁴
L-theanine (97 mg) + caffeine (40 mg)	44 (M=21.2, 18–34)	AS	Improved attention switching	Uncertain (no positive control)	Giesbrecht et al. (2010) ⁶⁵
L-theanine (100 mg) + caffeine (50 mg)	21 (M=26, 18–40)	Sustained Attention to Response Task (SART)	Compounds improved sustained attention separately, but combination cancelled out effects	No improvement	Foxe et al. (2012) ⁵⁸
L-theanine (200 mg) + caffeine (160 mg) vs. tea (not matching MX content)	20 male only (M=21.9, 21–23)	Simple Visual Reaction Time (SVRT), Recognition Visual Reaction Time (RVRT)	Combination improved attention, most notably on RVRT but not on SVRT, no effect of tea	Yes	Kahathuduwa et al. (2016) ⁵³

Combination	Subjects[Age]	Test	Outcome	Additive effects	Reference
High flavanol (520 mg/994 mg) cocoa beverage vs. matched control	30 (M=21.9, 18–35)	RVIP	994 mg CF beverage significantly improved RVIP response latencies but also increased error rate compared to control	Yes	Scholey et al. (2010) ³⁴
Cocoa beverages containing 400, 250 or 0 mg flavonoids	72 (40-65 years; 33.7% males)	RT, DV, Choice Reaction Time	No improvement of cognitive performance	No	Pase et al. (2013) ⁶⁶
Cocoa, caffeinated cocoa & caffeine (66 mg) only	23 (M=20.25, SD=2.23 years)	Bakan Dual task, Continuous Performance Test	Caffeinated cocoa lowered omission errors and improved accuracy compared to cocoa alone	Yes	Boolani et al. (2017) ⁶¹
Chocolate with high theobromine (250 mg) + caffeine (19 mg) or low theobromine (100 mg) + caffeine (8 mg) content	22 (M=35.4, SD=14.2; 18-70 years)	RT, RVIP	High MX content improved reaction time and RVIP performance (P<0.01), low MX content improved RVIP performance (P<0.05)	Yes	Smit, Gaffan & Rogers (2004) ⁶⁰

Abbreviations

AS = Attentional Switch, DV = Digit Vigilance, IA = Intersensory Attention, MT = Memory Task, RT = Reaction Time, RVIP = Rapid Visual Information Processing, RVRT = Recognition Visual Reaction Time, SART = Sustained Attention to Response Task, SVRT = Simple Visual Reaction Time

4.1.2. Executive function

Caffeine and L-theanine.

As outlined earlier, several studies found that caffeine and L-theanine improve attentional performance. Interestingly, the combination of caffeine and L-theanine appears to mainly improve attention scores in more complex, executive measures, such as AS accuracy,^{64,67} as well as reaction times in the delayed word recognition (DWR) task and accuracy in the sentence verification task (see Haskell et al.⁶²; Table 3). However, more studies need to be conducted to ascertain this potential mechanism.

Caffeine and chlorogenic acid.

Few clinical experiments have assessed interactions of MX and CGA on executive function. One study found that decaffeinated coffee with high CGA content improved working memory in healthy elderly (see Cropley et al.,⁵⁰; Table 3). However, Cropley et al.⁵⁰ did not assess the effect of high CGA content in caffeinated coffee. Hence it remains unclear to what extent CGA and caffeine have synergistic effects. These experiments do however show that coffee with normal CGA content has a stronger effect than decaffeinated coffee, independent of its CGA content.

Caffeine, theobromine and cocoa flavonoids.

Several studies assessed effect of cocoa or processed cocoa products such as chocolate or chocolate milk on attention. Early experiments by Smit et al. (2004)⁶⁰ found that normal portions of chocolate or cocoa had a measurable cognitive effect and that these were attributable to the methylxanthine content. Yet, a systematic review by Scholey and Owen from 2013⁶⁸ concluded that there is also evidence for an improvement of executive function 90-150 minutes after the administration of cocoa flavanols. Indeed, some studies have shown various different improvements of executive function from cocoa compared to caffeine.^{34,35} Whilst previous experiments of Scholey et al. (2010)³⁴ resulted in an improvement in the Serial Sevens task, a very recent, randomized, placebo-controlled trial by Boolani et al. (2017)⁶¹ reported null results

on the Serial Sevens.⁶¹ They did, however, report lower omission errors and improved accuracy on the Bakan primary task compared to caffeine alone. Possibly, these results were due to an anxiogenic effect of cocoa, which would be comparable to the reported beneficial effect of L-theanine when combined with caffeine. However, this added benefit of cocoa in combination with caffeine on attentional performance appears only to be measurable when the content of MX is increased sufficiently. For instance, two other studies assessing the effect of cocoa beverages containing up to 900mg of flavonoids did not find any significant improvement in attentional performance.^{42,66} However, it should be noted that these studies don't assess how MX contributes to the effects observed. Thus, the results are, at this point, not sufficient to draw any conclusion concerning the effect of cocoa flavonoids and MX on attentional performance.

Table 3. Additive effects of caffeine plus constituent compounds on executive function.

Combination	Subjects[Age]	Test	Outcome	Additive effects	Reference
L-theanine (250 mg) + caffeine (150 mg)	24 (M=21.3, 18–34)	Numeric Working Memory (NWM), Delayed Word Recognition (DWR), Sentence Verification	Improvement in NWM reaction time, DWR reaction time and sentence verification task accuracy	Yes	Haskell et al. (2008) ⁶²
L-theanine (97 mg) + caffeine (40 mg)	29 (M=30.6, 18-45)	Attentional switch (AS)	Improved task switching	Yes	Einöther et al. (2010) ⁶⁴
Caffeine (100 mg) + L-theanine (50 mg)	27 (M=28.3, SD=5.34)	AS, Memory task (MT)	Simultaneous increase in response speed and accuracy in AS, reduced susceptibility to distracting stimuli in MT	Yes	Owen et al. (2008) ⁶³
Theobromine (700 mg) + caffeine (40 mg)-	24 female subjects (M=51.1, SD=12.7)	Digital Symbol Substitution Test (DSST)	No treatment effect on DSST performance	No	Mitchell et al. (2011) ²⁹
High flavanol (520 mg/ 994 mg) cocoa beverage vs. matched control	30 (M=21.9, range 18–35)	Serial Threes and Serial Sevens Subtraction task (STS & SSS)	520 mg and 994 mg cocoa flavanol improved STS scores, 994 mg CF beverage increased errors in SSS	Yes, but no flavanol control	Scholey et al. (2010) ³⁴
Cocoa beverages containing 400, 250 or 0 mg flavonoids	72 (40-65 years; 33.7% males)	Immediate Word Recall, Spatial Working Memory,	No improvement of cognitive performance	No	Pase et al. (2013) ⁶⁶

		NWM, DWR, Delayed Picture Recognition			
Cocoa beverages containing 903 or 15 mg flavanols	12 male only (M=30)	Stroop Task	No significant behavioral effect	No	Decroix et al. (2016) ⁴²

Abbreviations, AS = Attentional Switch, DWR = Delayed Word Recognition, DSST = Digital Symbol Substitution Test, MT = Memory Task, NWR = Numeric Working Memory, STS = Serial Threes Subtraction Task, SSS= Serial Sevens Subtraction task

4.2. *Acute effects on mood*

Caffeine and L-theanine.

As reported above, Camfield et al.⁸ concluded that combining caffeine and L-theanine increases subjective alertness in several independent studies. Additionally, Haskell et al.⁶² found that a high (250 mg) dose of L-theanine combined with 150 mg of caffeine resulted in increased alertness and reduced symptoms of fatigue compared to caffeine only. Amongst two other studies involving lower doses (97 mg L-theanine + 40 mg caffeine), one did not find any change in self-reported mood compared to caffeine only (see Table 4). Another one had similar findings, though there was no control with caffeine only. Experiments by Rogers et al.⁶⁹ found that 250 mg caffeine and 200 mg L-theanine did not significantly reduce caffeine-induced jitteriness or other mood states. However, the combination did attenuate the caffeine-induced systolic and diastolic blood pressure. Moreover, L-theanine alone caused a decrease in anxiety as measured in the Visual Probe task. Given that L-theanine inhibits glutamate reuptake and stimulates GABA release in vitro, higher doses may antagonize the stimulatory effects of caffeine. The added fatigue and stress from complex attention tasks may be lessened by stress-alleviating effects of L-theanine. Yet, many of the available findings do not show such an effect. However, as suggested by Haskell et al.,⁶² other mechanisms, such as the effect of L-theanine on caffeine absorption, may interact further with the effect of caffeine. To elucidate the impact of L-theanine on caffeine absorption, it would be necessary to conduct a pharmacokinetic analysis comparing caffeine alone compared to caffeine + L-theanine at different doses of L-theanine.

Caffeine and chlorogenic acid.

CGA has been reported to have anxiolytic properties. Bouayed et al.⁴⁹ tested the effect of 20 mg/kg CGA on anxiety-related behavior in mice, and found an anti-anxiety effect that was similar to 1 mg/kg diazepam. This effect was reversed by flumazenil, which suggests that the effect of CGA was mediated by the GABA-A benzodiazepine receptor. In healthy elderly humans, decaffeinated coffee high in CGA improved some mood measures compared to decaffeinated coffee that was low in CGA.⁵⁰ Cropley et al.⁵⁰ found that decaffeinated coffee with

high (521 mg) CGA content increased “alertness” relative to decaffeinated coffee with regular (224 mg) CGA content in healthy elderly. However, these findings refer only to self-reported mood states, and these effects were slight compared to mood effects of caffeinated coffee with low CGA.

Whilst these experiments show that CGA may affect behavior, there is little research on the possible synergistic effect of CGA with caffeine. Given that CGA has been shown to have an inverted U-shaped dose-response curve in mice with an active dose at 20 mg/kg,⁴⁹ future studies should determine dose ranges most applicable for humans, with or without caffeine.

Caffeine and flavonoids.

In terms of mood effects cocoa flavonoids may modify caffeine’s psychoactive effects in a similar manner to L-theanine. Experiments by Boolani et al.⁶¹ found that combination of cocoa extract and caffeine attenuated the anxiety-provoking effects of caffeine alone. However, the combination did not affect mood or motivation in any other manner. Interestingly, experiments by Scholey et al.³⁴ tested cocoa extracts at two different concentrations of flavanols (520 mg/994 mg), but only the lower dose reduced self-reported mental fatigue compared to a control beverage with matching MX content.

Experiments on the self-reported mood effects of 300 mg EGCG found an increase in calmness and lower mental stress compared to subjects receiving a placebo.⁴³ Hence EGCG may reduce the negative mood effects of caffeine in a similar manner to L-theanine. Indeed, Park et al.⁷⁰ found that EGCG reverses caffeine-induced anxiogenic-like effects in mice. Overall, data on EGCG psychoactive interactions with MX are sparse, and the above effects need to be confirmed.

Theobromine-caffeine interactions.

Mitchell et al.²⁹ found that a combination of a high (700 mg) dose of theobromine combined with 40 mg of caffeine caused similar effects on mood as caffeine alone. Interestingly, subjects receiving a combination of the MX did not exhibit an increase in blood pressure that occurred with the consumption of caffeine alone. These findings are similar to some study outcomes of

caffeine and L-theanine combinations. However, as described previously, the combination of theobromine and caffeine exerted effects on reaction time and attention at very low doses of caffeine (8-20 mg) suggesting that theobromine may be selectively enhancing caffeine psychoactivity.⁶⁰ These experiments found that the MX increased “energetic arousal” as well. The peak of the mood effects was also delayed in subjects receiving cocoa powder plus MX compared to subjects receiving only the MX. In view of the limited data available theobromine combined with caffeine has slight synergistic efficacy on mood compared to theobromine or caffeine alone.

Table 4. Additive effects of caffeine plus constituent compounds on self-reported mood and alertness.

Combination	Subjects[Age]	Test	Outcome	Additive effects	Reference
Caffeine (250 mg) + L-theanine (200 mg)	48 (M=20.5 SD 2.0)	Self-reported jitteriness, alertness, and mood. Visual probe task	L-theanine did not reduce self-reported jitteriness, alertness	No	Rogers et al. (2008) ⁶⁹
L-theanine (250 mg) + caffeine (150 mg)	24 (M=21.3, 18–34)	Bond-Lader mood assessment	Increased 'alert' and reduced fatigue ratings	Different than anticipated	Haskell et al. (2008) ⁶²
L-theanine (97mg) + caffeine (40mg)	29 (M=30.6, 18–45)	Bond-Lader mood assessment	No improved subjective alertness	No	Einöther et al. (2010) ⁶⁴
L-theanine (97mg) + caffeine (40mg)	44 (M=21.2, 18–34)	Bond-Lader mood assessment	Increase in subjective alertness and reduced self-reported tiredness	Uncertain (no caffeine control)	Giesbrecht et al. (2010) ⁶⁵
High flavanol (520 mg/994 mg) cocoa beverage vs. matched control	30 (M=21.9, 18–35)	Mental fatigue VAS	Only 520 mg CF attenuated self-reported 'mental fatigue', no effect on anxiety	Yes, but no flavanol only control	Scholey et al. (2010) ³⁴
Cocoa beverages containing 400, 250 or 0 mg flavonoids with matched caffeine (40mg) and theobromine (240mg) content	72 (40-65 years; 33.7% males)	Bond-Lader mood assessment	Increased self-rated calmness and contentedness relative to placebo after 30 days. No acute effects	Yes, but only acute	Pase et al. (2013) ⁶⁶
Cocoa, caffeinated cocoa & caffeine (66 mg) only	23 (M=20.25 SD 2.23)	Mood and motivation questionnaire	Attenuation of caffeine-induced anxiety effects, no other effect on mood or motivation	Yes	Boolani et al. (2017) ⁶¹

Combination	Subjects[Age]	Test	Outcome	Synergy	Reference
Theobromine (250 mg) + caffeine (19 mg) vs. 11.6 g cocoa with matching MX content	20 (M=32.6 SD 11.2)	Mood construct	Increased self-reported energetic arousal and hedonic tone (only marginally for cocoa)	Yes	Smit, Gaffan & Rogers (2004) ⁶⁰ - Study 1
Chocolate pieces with either high theobromine (250 mg) + caffeine (19 mg) or low theobromine (100 mg) + caffeine (8 mg) content	22 (M=35.4 SD 14.2; 18–70)	Mood construct	No effect: MX-containing treatments were not significantly different from white chocolate	No	Smit, Gaffan & Rogers (2004) ⁶⁰ - Study 2
Theobromine (250 mg) + caffeine (19 mg) vs placebo, both consumed together with 'novel' drink	64 (M= 21.1 SD 2.2)	Liking of chocolate	Addition of MX increased liking of drink	Uncertain	Smit & Blackburn (2005) ³¹
Theobromine (700 mg) + caffeine (40 mg)	24 female subjects (M=51.1 SD=12.7)	Bond-Lader mood assessment	Combination had similar effects as caffeine alone on mood (increased self-rated alertness)	No	Mitchell et al. (2011) ²⁹
High (521 mg) vs. low (224 mg) CGA decaf coffee	39 light coffee drinkers (M=62.5, SD=6.0, 53–	Mood questionnaire	High CGA content increased self-reported alertness	Uncertain	Cropley et al. (2012) ⁵⁰

	79 years)				
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4.3. *Physiological measurements*

Caffeine and L-theanine.

Caffeine and L-theanine appear to interact in terms of brain activity as shown via EEG readings. Specifically, L-theanine consumption results in an increase in alpha-wave activity,⁶⁷ whereas caffeine reduced alpha-activity at a dose of 50 mg in experiments by Foxe et al.⁵⁸ Nevertheless, L-theanine did not have any significant effect at a dose of 100 mg. Other studies that combined L-theanine and caffeine at levels and ratios equivalent to 1-2 cups of tea found that the compounds eliminated the vasoconstrictive effect and behavioral effects of caffeine.⁷¹ All in all, these findings support the theory that L-theanine affects electrical activity in the brain, which is also the case for caffeine. The studies show that there is an interaction of caffeine and L-theanine, yet it is unclear in what way it alters the impact of caffeine itself.

Caffeine, theobromine and flavonoids.

Improved blood flow and endothelial function from flavanol-mediated nitric oxide production could improve nutrient and oxygen delivery to the brain. Indeed, several MX and phytochemical combinations have been shown to affect physiological function, as indicated by event-related potentials or cerebral blood flow (see Table 5). As mentioned previously, EGCG reverses caffeine-induced anxiogenic-like effects in mice. This effect correlated with an attenuation of caffeine-induced increase of lower density-ratios of fast and slow EEG frequency spectrum bands.⁷⁰ Experiments on postmenopausal women found that dark chocolate intake improved vascular endothelial function and reduced cerebral blood flow responses.⁷² However, these experiments did not report parallel changes in cognitive performance.

Theobromine has been shown to interact with flavonoids as well: recent experiments by Sansone et al.⁷³ demonstrated that the MX may enhance cardiovascular effects of cocoa flavanols via accelerated absorption. When healthy subjects received cocoa flavanols combined with MX, epicatechin AUC was significantly higher than the same dose of flavanols only. As mentioned earlier, coadministration of 700 mg theobromine has been shown to lower blood pressure and to attenuate caffeine-induced increase in blood pressure.²⁹ While experiments by van den Bogaard

et al.⁷⁴ found that theobromine-enriched cocoa reduced systolic blood pressures and elevates 24-hour systolic blood pressure; in contrast, traditionally processed cocoa powder did not cause any changes in blood pressure. According to Baggott et al.²⁶ the increase in systolic blood pressure is prevented in subjects with the G allele of rs4822492. These results indicate theobromine's influence on blood pressure effects from caffeine or cocoa flavanols.

Table 5. Additive effects of caffeine plus constituent compounds on acute physiological effects.

Combination	Subjects[Age]	Test	Outcome	Additive effects	Reference
Caffeine (250 mg) + L-theanine (200 mg)	48 (M=20.5, SD=2.0)	Blood pressure	L-theanine attenuated a caffeine-induced increase in blood pressure	Yes	Rogers et al. (2008) ⁶⁹
Caffeine (75 mg) + L-theanine (50 mg)	24 (M= 21.8, SD=3.19)	Blood pressure and cerebral blood flow	L-theanine attenuated effects of caffeine on vasoconstriction and cerebral blood flow	Yes	Dodd et al. (2015) ⁷¹
L-theanine (100 mg) + caffeine (50 mg)	16 (M=27.5, 21–40)	EEG background and event-related potential	Lower overall tonic alpha power, no significant change in alpha event-related potential	Yes	Kelly et al. (2008) ⁷⁵
L-theanine (97 mg) + caffeine (40 mg)	44 (M=21.2, 18–34)	Blood pressure	L-theanine did not attenuate a caffeine-induced increase in blood pressure	No	Giesbrecht et al. (2010) ⁶⁵
L-theanine (200 mg) + caffeine (160 mg) vs. tea	20 male only (M=21.9, 21–23)	Event-related potentials	Only L-theanine + caffeine resulted in significantly larger mean N2-P300 amplitude	Yes	Kahathuduwa et al. (2016) ⁵³
Theobromine (700 mg) + caffeine (40 mg)	24 female only (M=51.1, SD=12.7)	Blood pressure	Coadministration of theobromine attenuated the effect of caffeine on blood pressure.	Yes	Mitchell et al. (2011) ²⁹

Combination	Subjects [Age]	Test	Outcome	Additive effects	Reference
494 mg vs. 23 mg flavanol with matching MX content	18 (M=61, 55–65 years)	Cerebral blood flow (CBF) (fMRI) in older subjects	Increased perfusion in anterior cingulate cortex and central opercular cortex of parietal lobe.	Uncertain (no MX control)	Lamport et al. (2015) ⁴⁰
High (80%, vs. low (35%) cocoa chocolate	12 women (M=57.3, SD=5.3)	Cerebral blood flow (CBF) and brachial artery flow-mediated dilation (FMD) in women	Lower CBF responses during cognitive tasks & enhanced vascular endothelial function in terms of FMD	Uncertain	Marsh et al. (2017) ⁷²
Cocoa flavanols (0-820 mg) and MX (0-220 mg)	47 men (M=25.1 ± 2.3)	Cardiovascular effects and plasma concentrations	Combination increased epicatechin AUC and cardiovascular effect of cocoa flavanols.	Yes	Sansone et al. (2017) ⁷³
Coffee with 89 mg or 310 mg CGA	15 (M=26.3 ± 1.6)	Flow-mediated dilation	Improved vascular function which paralleled with 5-caffeoylquinic acid plasma concentrations	Yes, effect greater than in CGA only	Mills et al. (2017) ⁷⁶
Coffee, black tea extract, water with matched caffeine (100 mg)	16 subjects 8 male (M=36.9, SD= 6.3), 8 female (M=34.4, SD=11.8)	Heart rate, skin conductance & temperature	Skin temperature increase greater from coffee than from tea and water.	Possibly	Quinlan, Lane & Aspinall (1997) ⁷⁷

4.4. *Chronic effects*

Overall, the scientific consensus on the chronic (>8 weeks) health effects of coffee, tea, cocoa, and caffeine are largely in favor of consuming MX and associated polyphenols.^{78–80} However, at this stage, the main conclusion that can be drawn from these studies is that MX and polyphenol consumption is generally safe and correlates with a reduced risk of mortality and certain disorders. Recently, an umbrella review by Poole et al.⁷⁸ found that coffee consumption reduced overall mortality, as well as the risk of disorders, such as Parkinson's disease and depression. This beneficial effect applied partially also to decaffeinated coffee consumption, where users exhibited lower risks of Alzheimer's disease and depression. A review of six prospective cohort studies by Arab et al.⁷⁹ assessing the protective effect of caffeinated beverages on cognitive decline found that ameliorated risk was evident in all studies, particularly for tea consumption, but also for coffee and total caffeine intake.

Gender appears to play a considerable role in the beneficial effects of caffeine, given that prospective studies found that the beneficial effects of caffeine and other phytochemicals in coffee and tea are stronger in women than in men (review see Panza et al.⁵). A longitudinal ageing study in Singapore assessing cognitive decline in a Chinese cohort (≥ 55 years) found that tea consumption reduced risk of neurocognitive disorders after 1–2 years of monitoring.⁸¹ These effects were more predominant in regular consumers and greater in black (fermented) and oolong (semi-fermented) tea. A follow-up study of 957 subjects of this cohort found that the beneficial effects were only visible in consistent tea consumers and that the risk of neurocognitive disease was only reduced amongst women and carriers of the apolipoprotein e4-gene.⁸²

Longitudinal studies on the protective effect of tea against age-related cognitive decline concur with other research assessing the neuroprotective properties of polyphenols.⁸³ By reducing oxidative stress and neuroinflammation, polyphenols found in tea, coffee, grapes and berries may not only reduce the risk of age-related cognitive decline but also improve brain function in elderly.⁸⁴ Interestingly, coffee consumption appears to have more beneficial chronic effects than isolated caffeine. Experiments by Shukitt-Hale et al.⁵⁷ have shown that 8-week administration of coffee, but not caffeine, caused an improvement in a working memory task (MT) and in psychomotor performance.

Cocoa consumption has been linked to lower risk of cognitive decline as well. A recent prospective cohort study assessing this association found a significant protective effect of chocolate intake.⁸⁵ Brickman et al.⁴¹ found that a 3-month high cocoa-flavanol diet

improved cognitive scores in 50-69 year old subjects, which correlated with an increase in dentate gyrus function. In the CoCocoa study, 90 elderly subjects given high flavanol/methylxanthine cocoa beverages demonstrated improved verbal fluency and executive function, with parallel improvements in insulin resistance and blood pressure compared to those drinking a low flavanol cocoa drink. However, the role of methylxanthines in these effects is unknown, since the low flavanol drinks also contained similar levels of methylxanthines.^{86,87} Interestingly, subjects consuming more than 75 mg of caffeine per day did not experience any protective effects, however, it is unclear what roles particular sources of caffeine or other dietary components played in this finding.⁸⁸ Sokolov et al.⁸⁹ outlined two main mechanisms that are most likely responsible for the beneficial effects of cocoa flavanols against age-related cognitive decline. Firstly, flavanols might exert neuroprotective effects via neuronal growth factors and promotion of neurogenesis. For instance, randomized-controlled trials by Neshatdoust et al.⁹⁰ found that a cocoa flavanol intervention for 12 weeks correlated with increased BDNF levels and better cognitive performance.

The role of theobromine in the neuroprotective effects of cocoa has not been elucidated. Yet, some findings suggest that it may have beneficial properties as well. For instance, a study on potential Alzheimer's disease biomarkers found that theobromine, but not caffeine, correlated with lower plasma A β 42 levels in subjects.⁹¹ Similarly, a study by Fernandez-Fernandez et al.⁹² on mice exhibited lower age-related cognitive decline when receiving a diet supplemented with theobromine, polyphenols, and polyunsaturated fatty acids. Moreover, recent experiments by Yoneda et al.²⁵ found that a 30-day supplementation of theobromine improved motor learning in mice, which correlated also with an upregulation of cAMP/CREB/BDNF pathways. Future studies are needed to examine the individual roles of theobromine and cocoa flavanols in terms of cognitive performance and biomarkers of brain health.

5. Conclusion

All in all, this review reveals the commonality that MX plants exert a stronger pro-cognitive effect when their natural composition of phytonutrients is maintained. Constituent compounds such as flavonoids and chlorogenic acid are more concentrated in the fresh leaves and beans of the plants compared to the processed product. Many of the studies have shown that the interaction of some of the phytochemicals results in greater improvement in neurocognitive function than from caffeine alone. Yet, the amount of studies directly assessing an acute synergistic effect of a compound with caffeine or theobromine by comparing the effect to caffeine alone is still scarce. Moreover, some of the studies, even on more well-known combinations such as caffeine and L-theanine, failed at reproducing the same results as in other studies. Though this should not keep us from investigating these phytochemicals. Proving that a treatment can enhance cognitive function in a statistically significant manner can be very hard, especially when only a small fraction of the population benefits a lot from that treatment. For instance, L-theanine appears to be most beneficial in subjects that reported being more stressed and/or anxious during the study. Thus, further research is needed in order to solidify the available evidence and to find out at what doses and ratios these phytochemicals exert the strongest acute effect on mood and cognition.

It should also be noted that this analysis did not encompass all sources of methylxanthines, nor all constituent phytochemicals. For instance, the role of other phytonutrients that are in cocoa and tea, such as quercetin, should be analyzed more in depth. We did also not include any research on guarana or kola nuts in this paper. Given that especially guarana is a popular ingredient in energy drinks, further research should address the role of its constituent phytochemicals.

Although there is a growing body of literature revealing chronic procognitive and/or neuroprotective effects of MX plants, the role of the specific constituent phytochemicals remains unclear. This paper has outlined possible anti-aging effects of some compounds, yet there are no longitudinal place-controlled cohort studies that would allow us to draw a conclusion on the beneficial chronic effect of some of these chemicals on neurocognitive function, let alone of their possible synergistic interaction. Cognitive decline becomes an emergent threat in many Western countries due to the aging of the population. The available literature allows us to conclude that the consumption of the most common sources of MX does, with some minor exceptions, no additional harm. These insights pave the way for randomized, double-blind longitudinal studies. This will allow us to find out what foods and

beverages, as well as what specific phytochemicals are particularly promising for promoting and maintaining brain health.

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ACCEPTED MANUSCRIPT

Highlights

- Coffee, tea, mate, guayusa, and cocoa contain various beneficial phytochemicals
- Methylxanthine + phytochemical interactions often superior to caffeine alone
- Numerous positive effects on mood and cognition, both acutely and chronically
- L-theanine and polyphenols such as flavonoids and chlorogenic acids most promising
- Available research requires replication; longitudinal cohort studies still missing